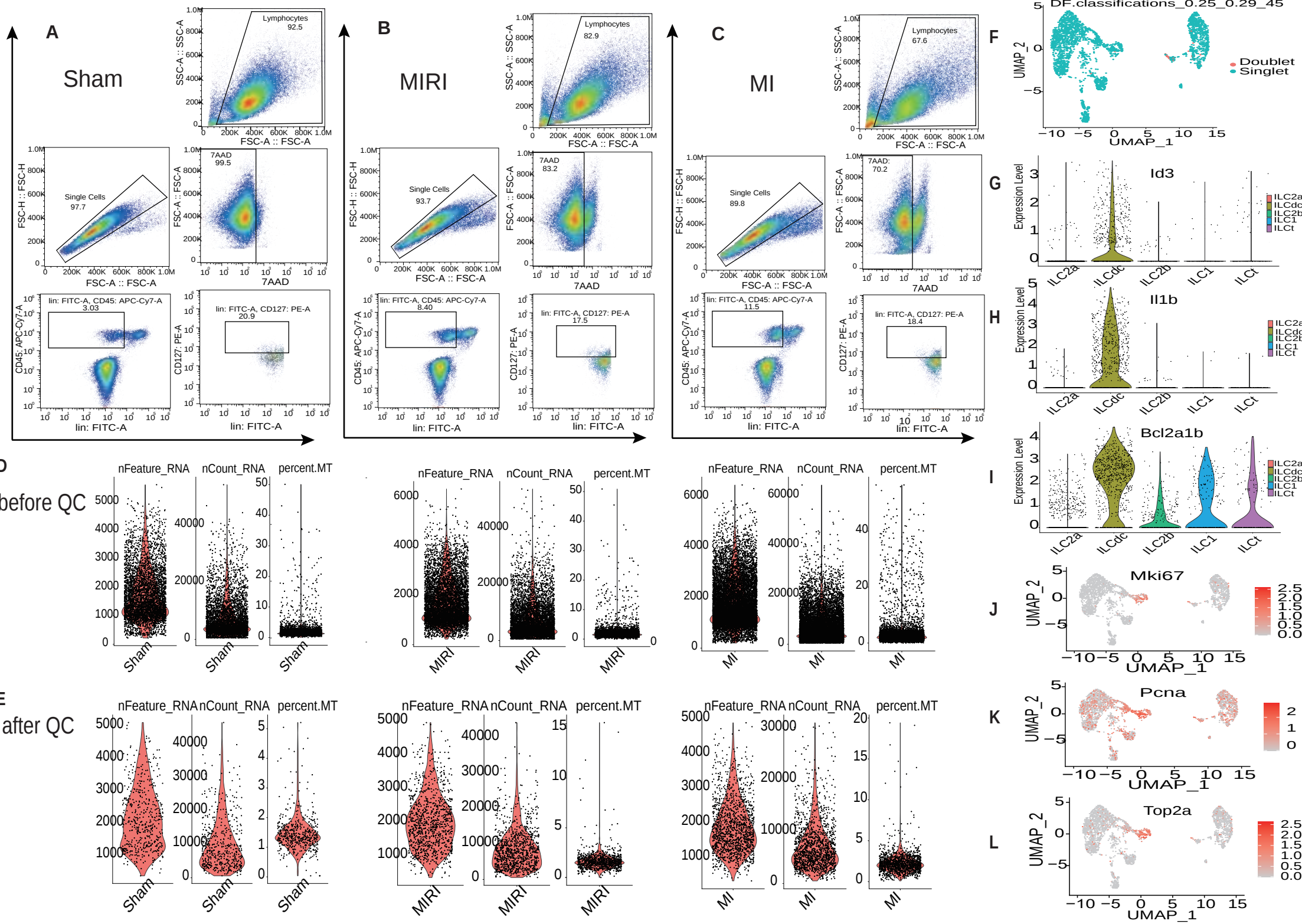
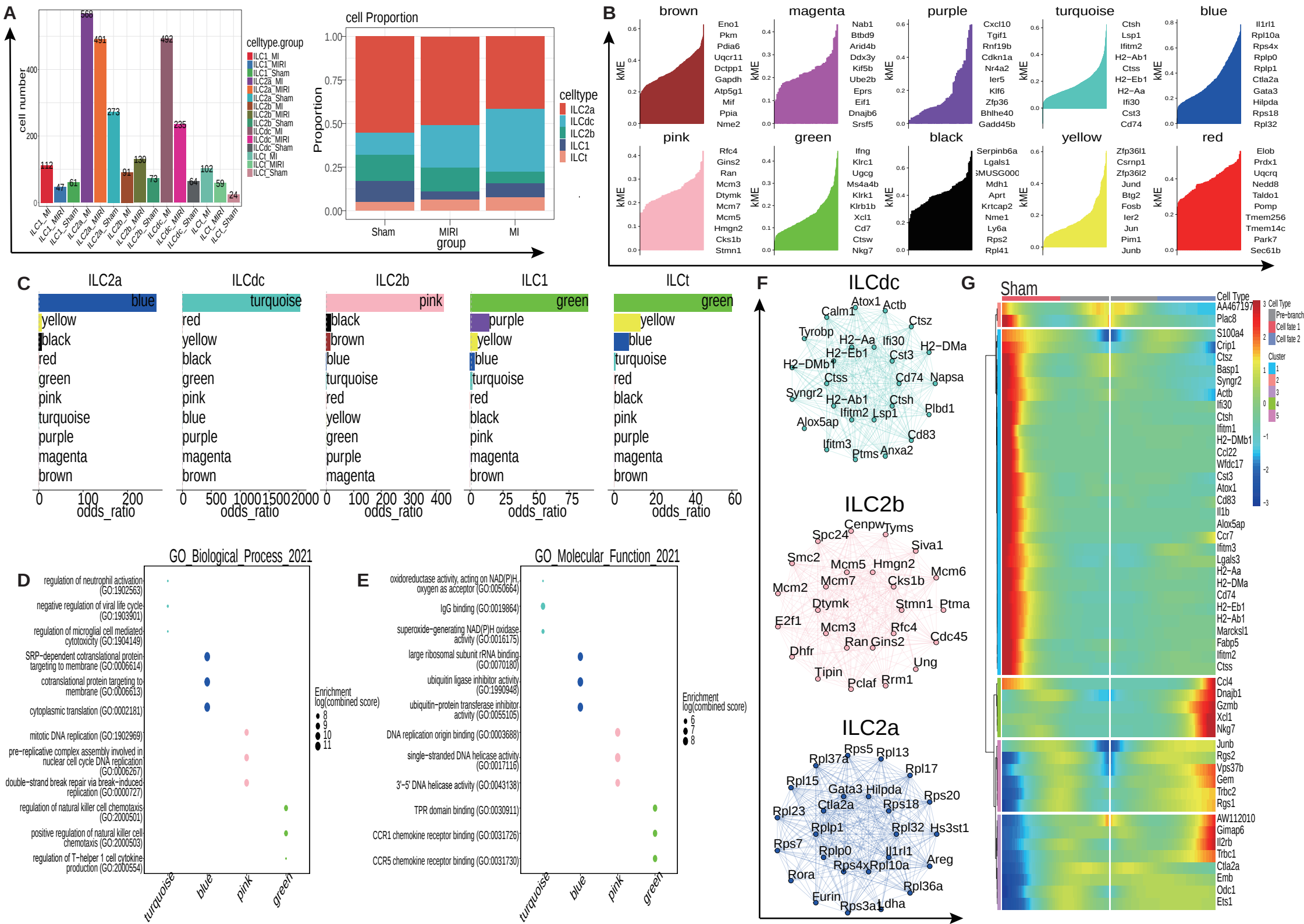
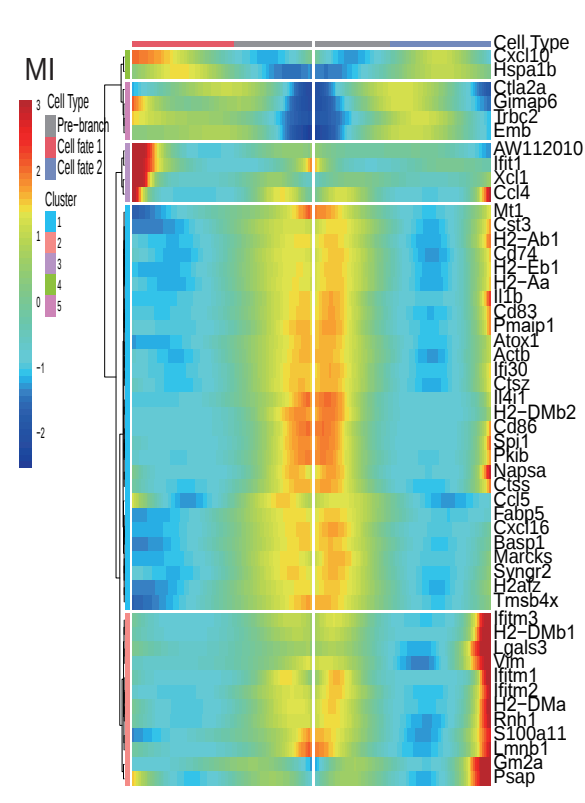
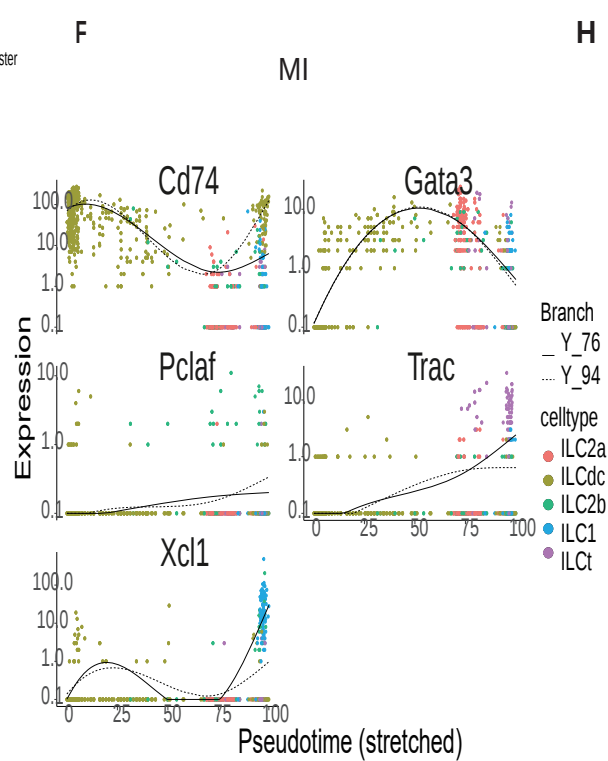
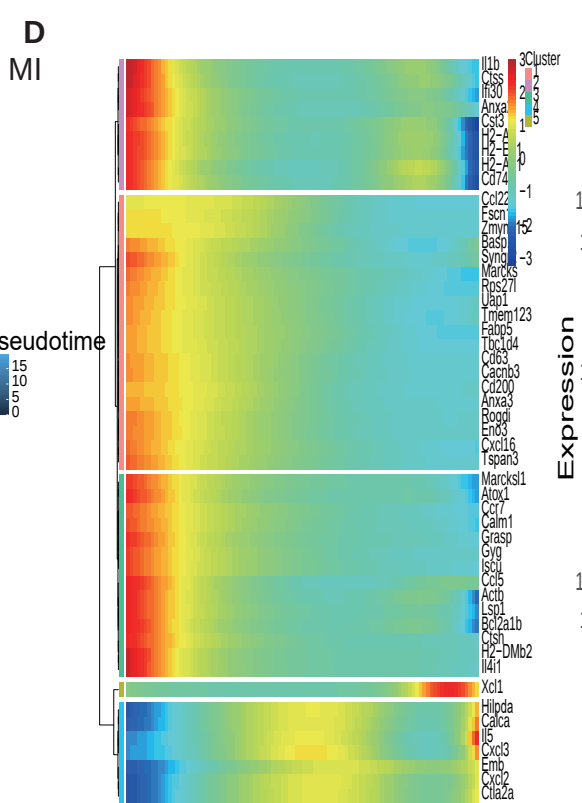
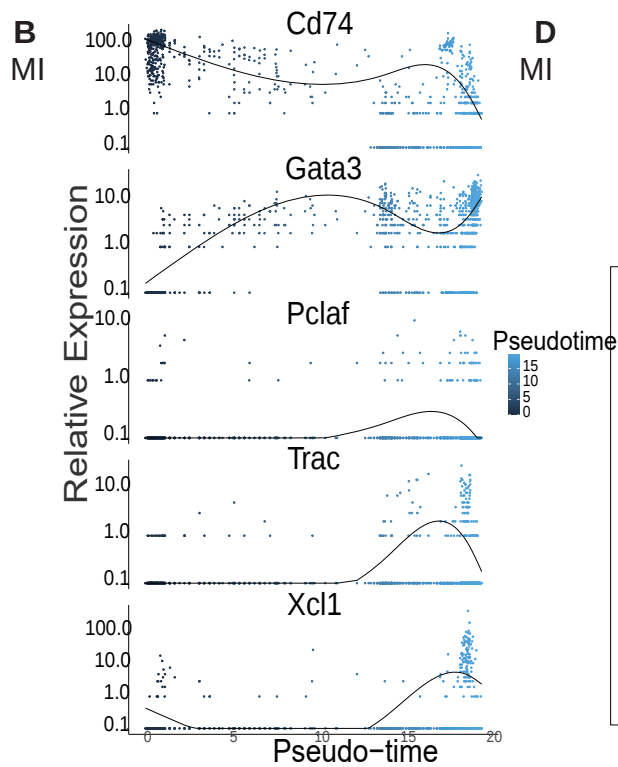
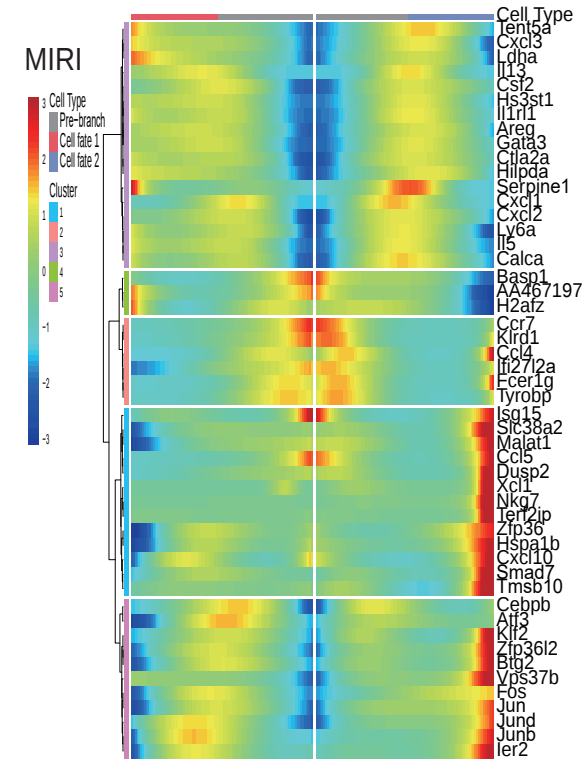
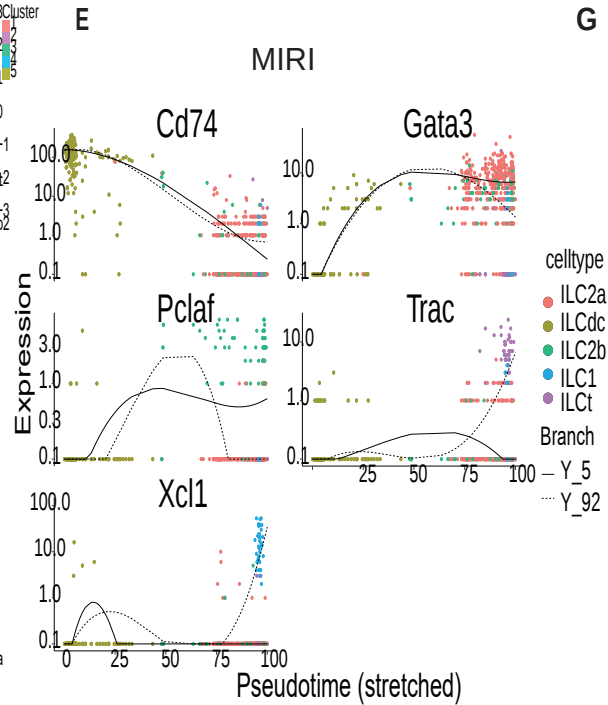
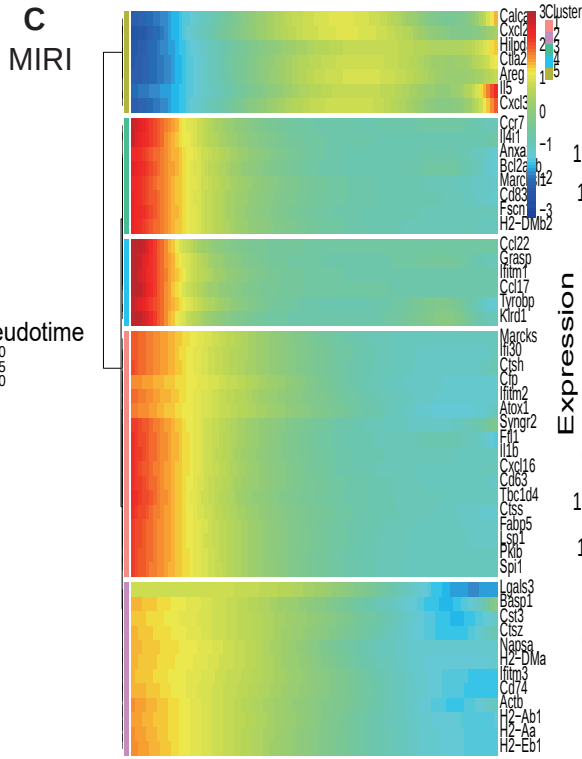
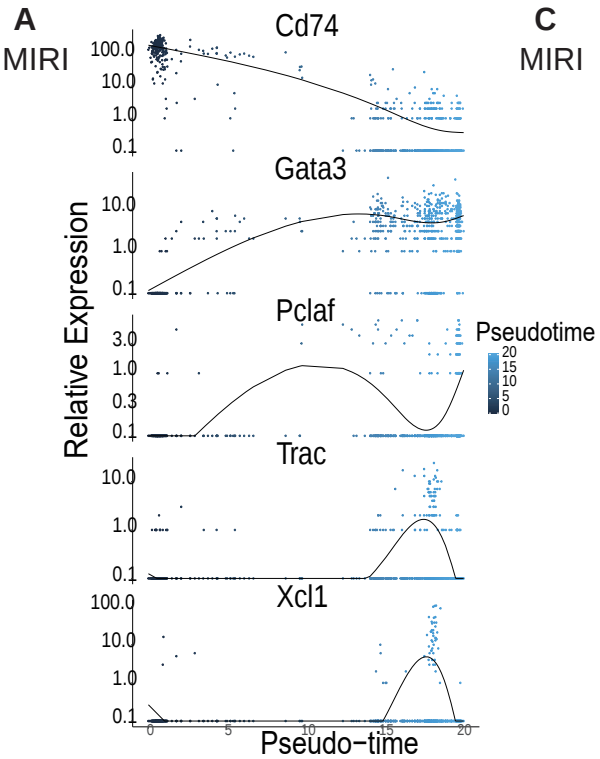


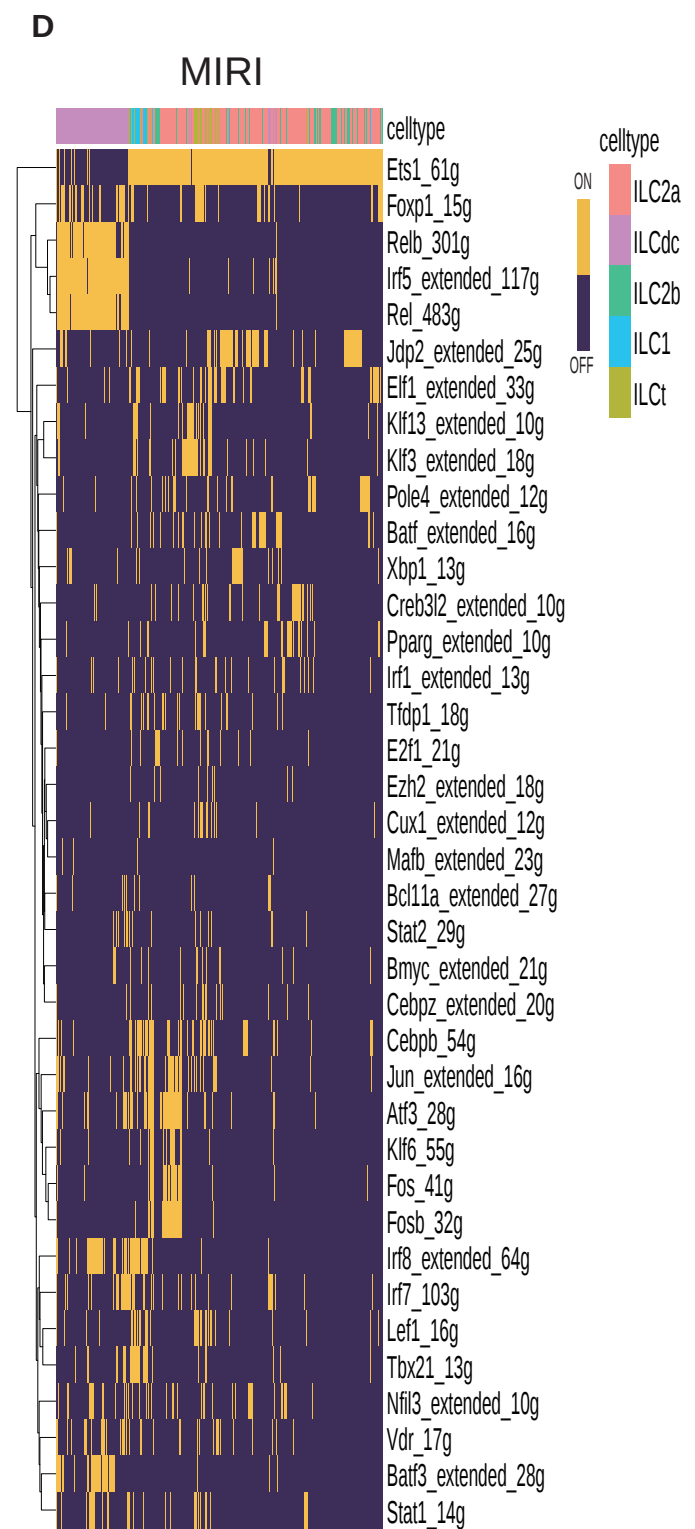
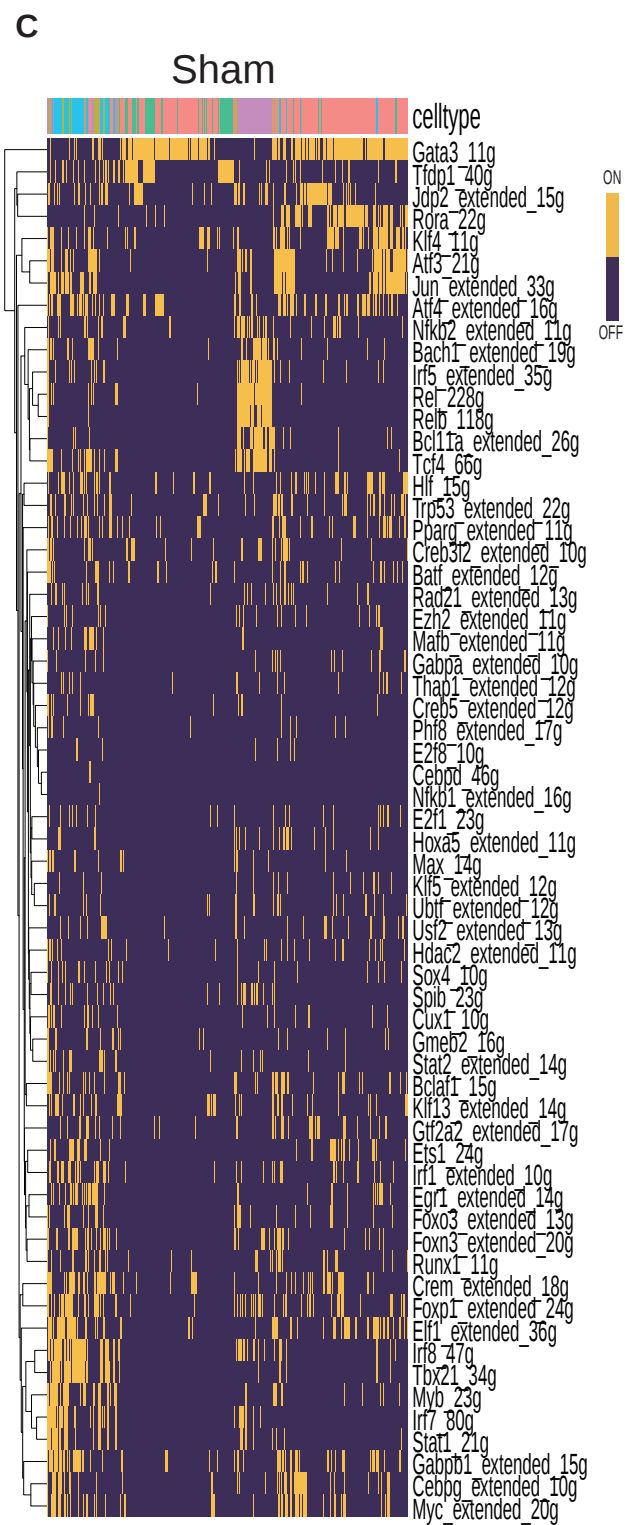
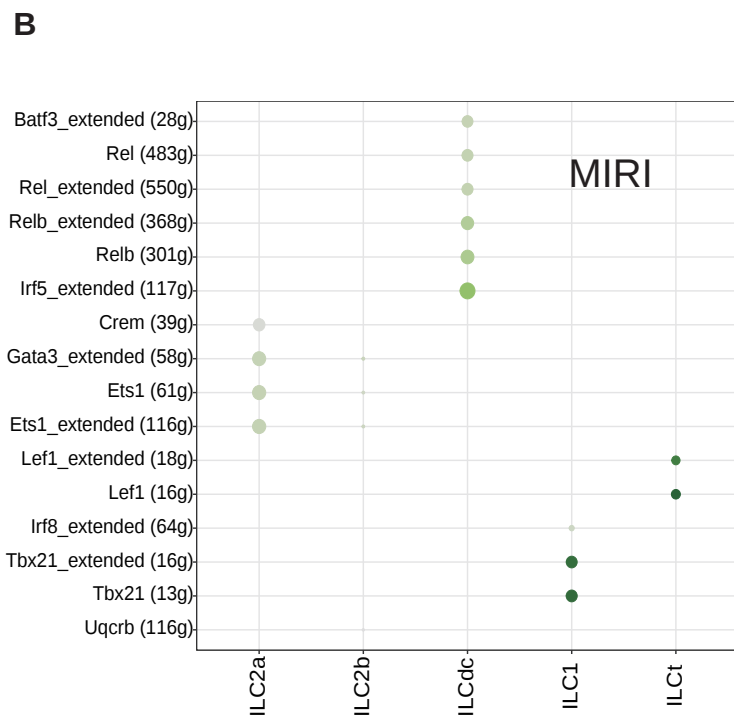
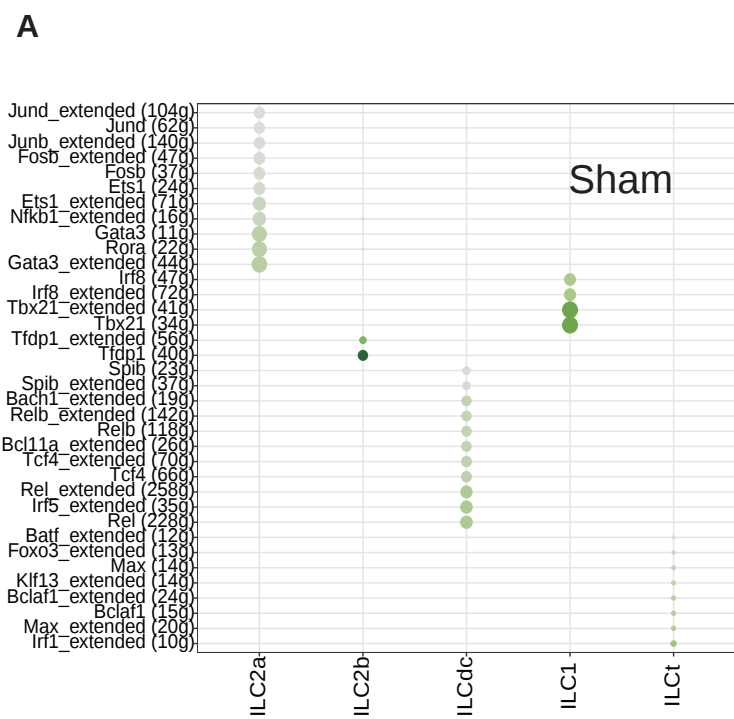
Abbreviations

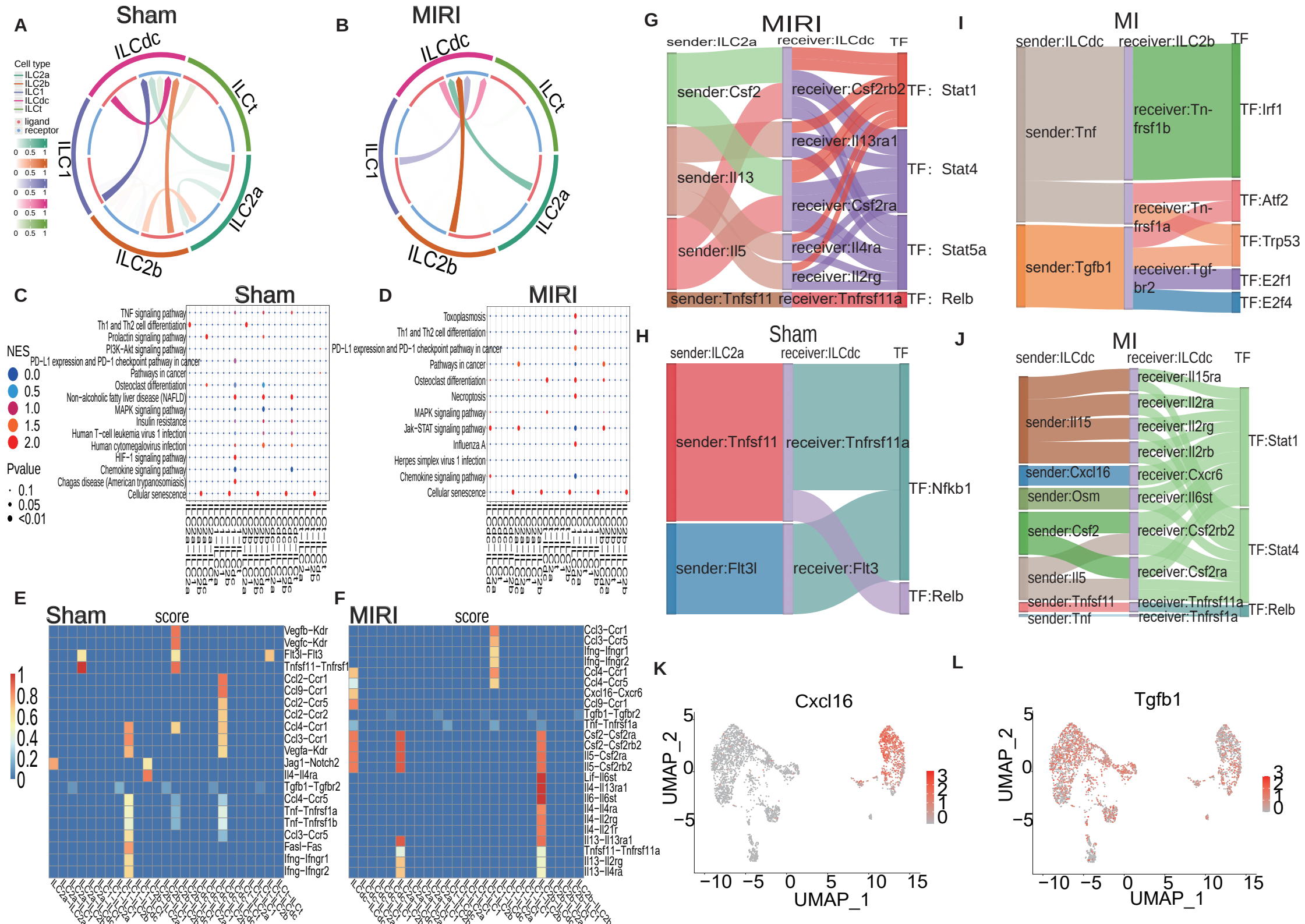
ILCs: innate lymphoid cells; MI: myocardial infarction; MIRI: myocardial ischemia-reperfusion injury; scRNA-seq: single-cell RNA sequencing; PCI: percutaneous coronary intervention; NK: natural killer cells; T-bet: T box transcript factor; ROR α : retinoic acid receptor-related orphan receptor- α ; GATA3: GATA binding protein 3; LTi: lymphoid tissue inducer; STEMI:ST-segment elevation myocardial infarction; IRI: ischemia-reperfusion injury; FACS: fluorescence-activated cell sorter; UMAP: uniform manifold approximation and projection; Id2: Inhibitor of DNA-binding protein 2; DCs: dendritic cells; Lef1: lymphoid enhancer-binding factor 1; DEGs: different expression genes; GSVA:Gene Set Variation Analysis; hdWGCNA: high dimensional weighted gene co-expression network analysis; SCENIC: single-cell regulatory network inference and clustering; GSEA: Gene Set EnrichmentAnalysis; KEGG: Kyoto Encyclopedia of Genes and Genomes; TFs: Transcription factors; L-R-T: ligand-receptor-transcription factor; ILCFR: follicular regulatory ILCs; LAD: left anterior descending coronary artery; PCA: principal component analysis; SNN: Shared nearest neighbor algorithm; KNN: k-Nearest Neighbors algorithm.





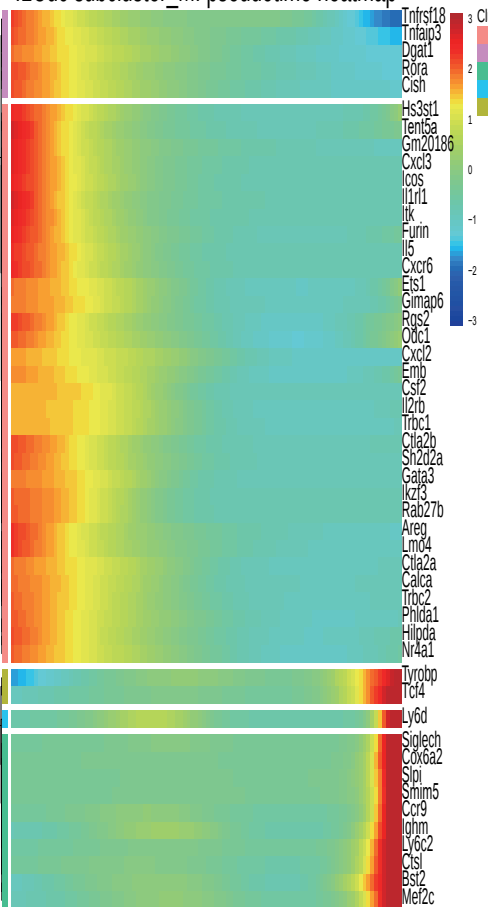






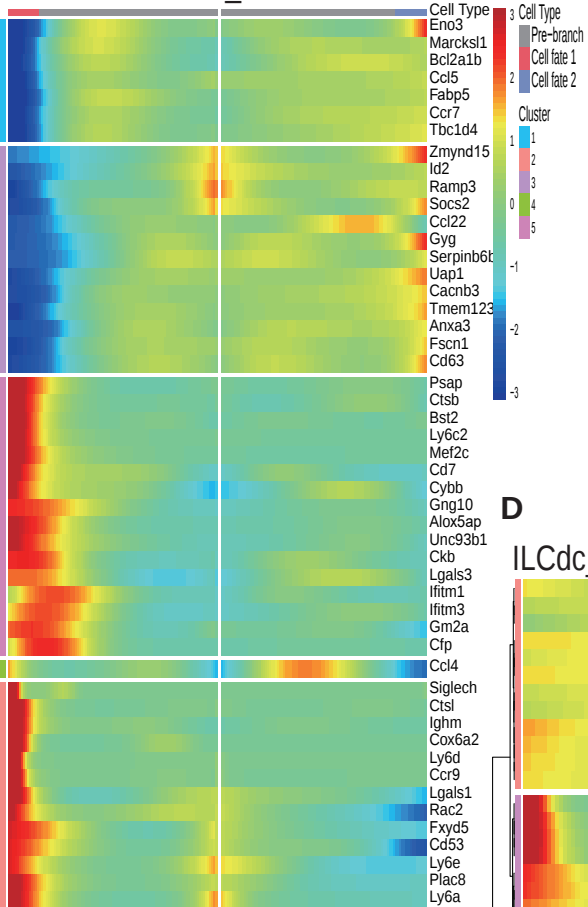
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ILCdc subcluster_MI pseudotime heatmap

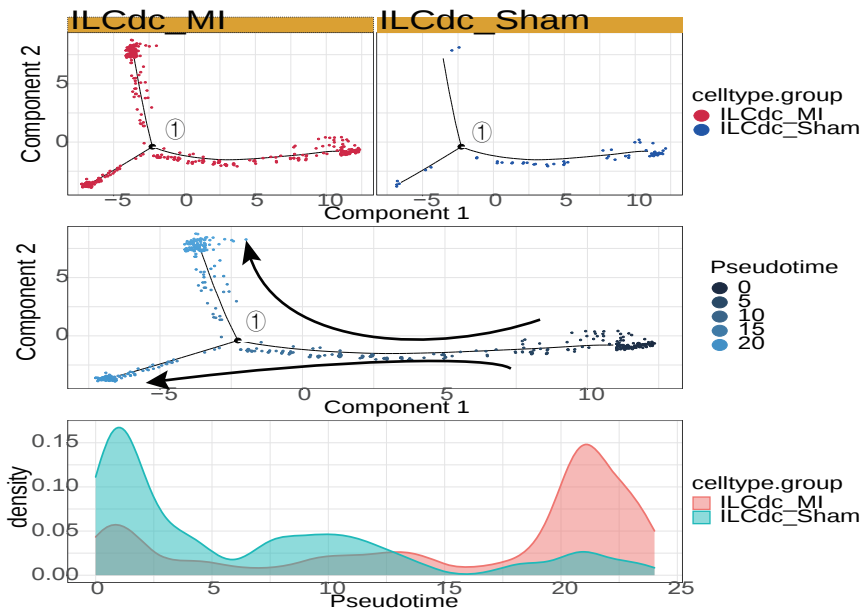


B

ILCdc subcluster_MI BEAM

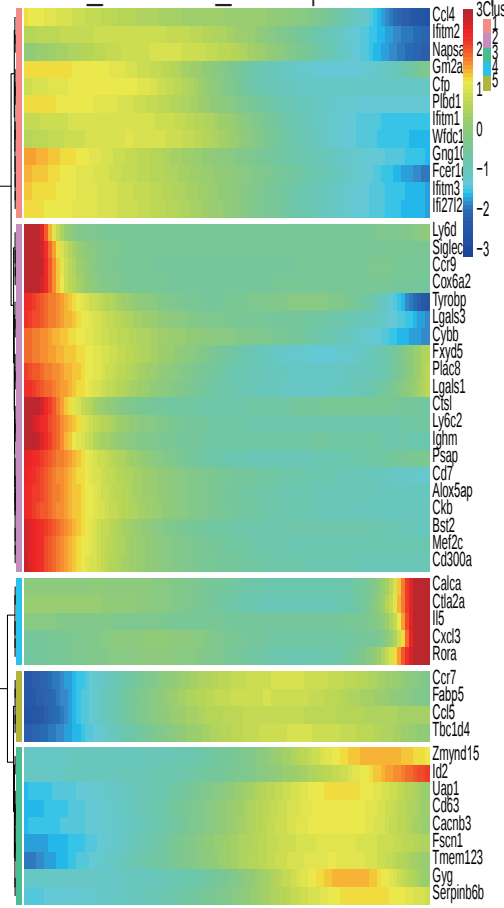


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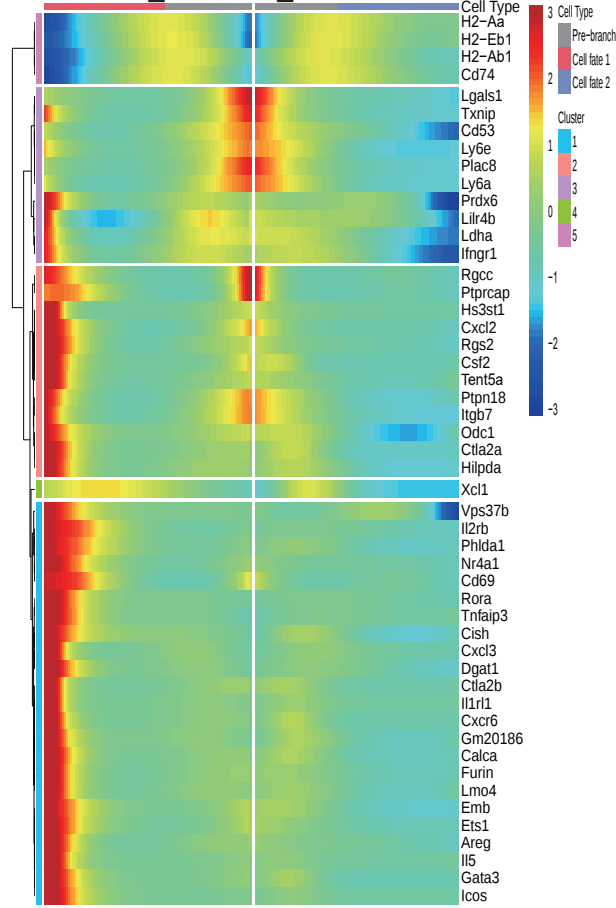
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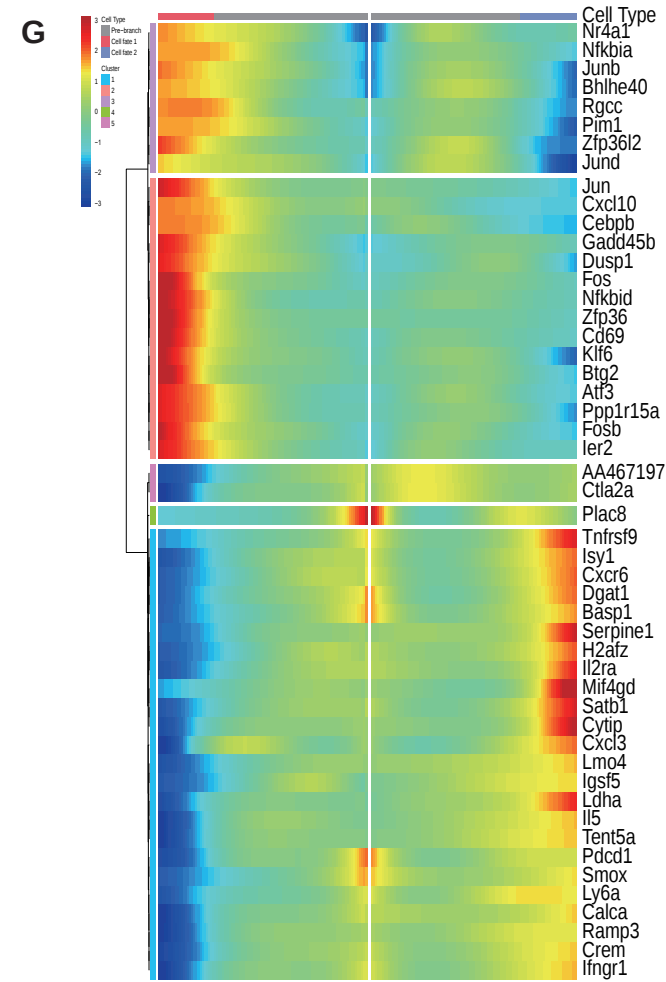
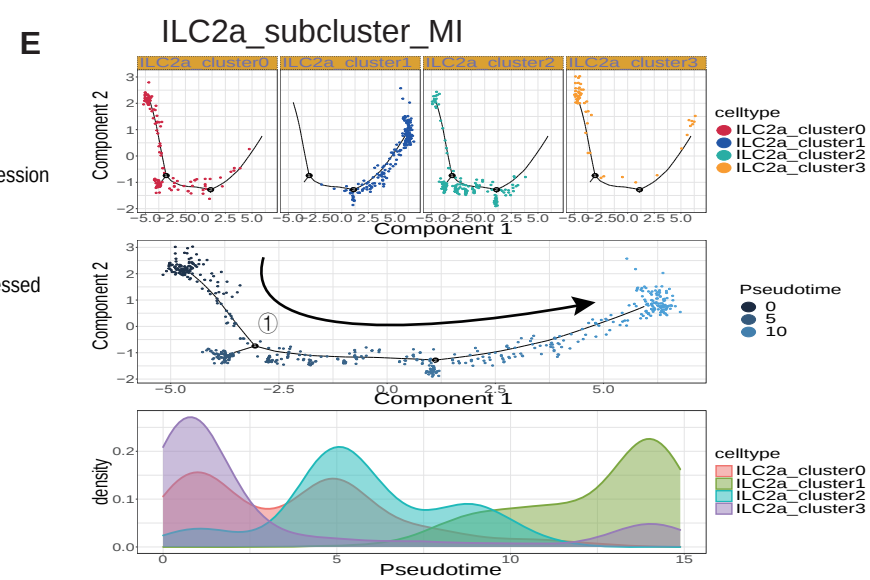
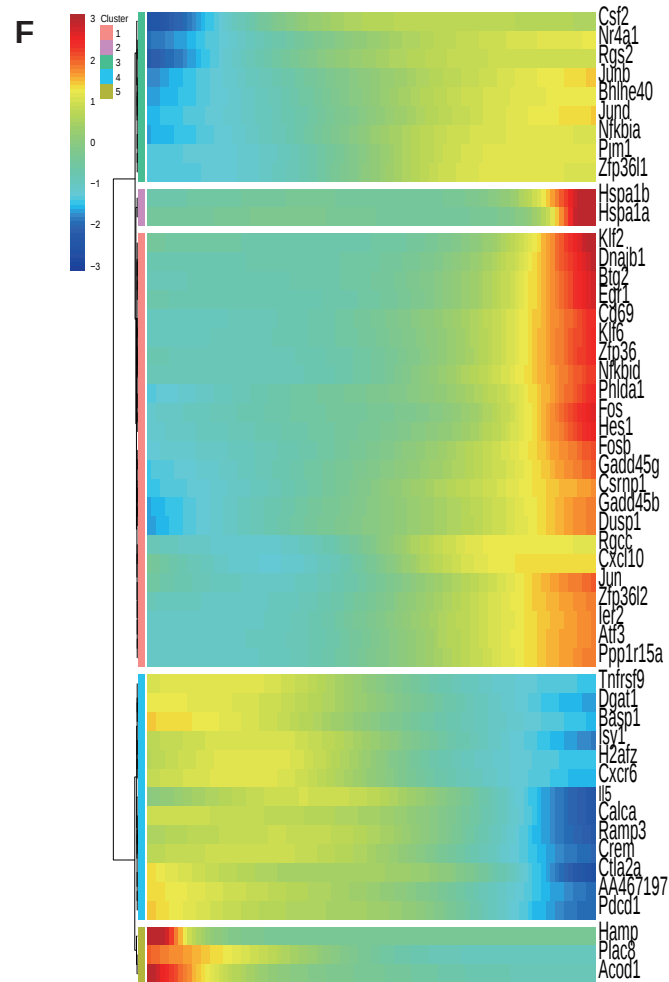
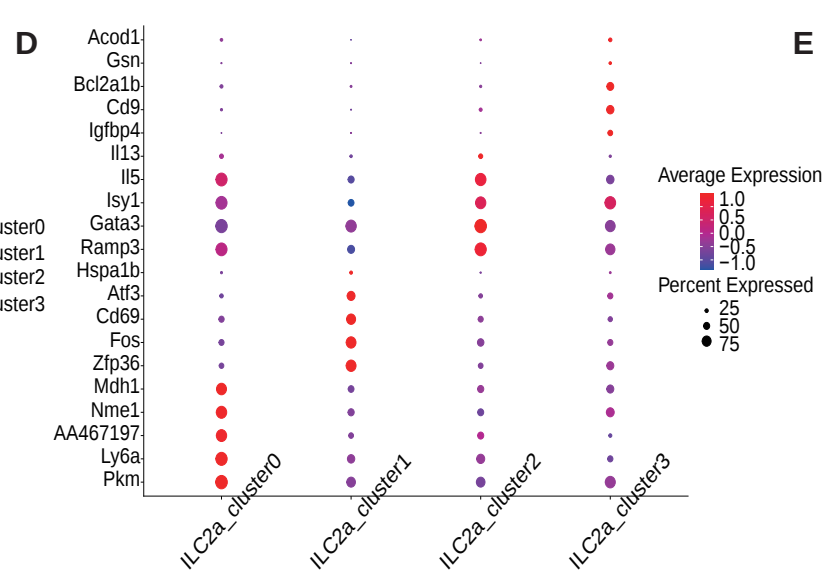
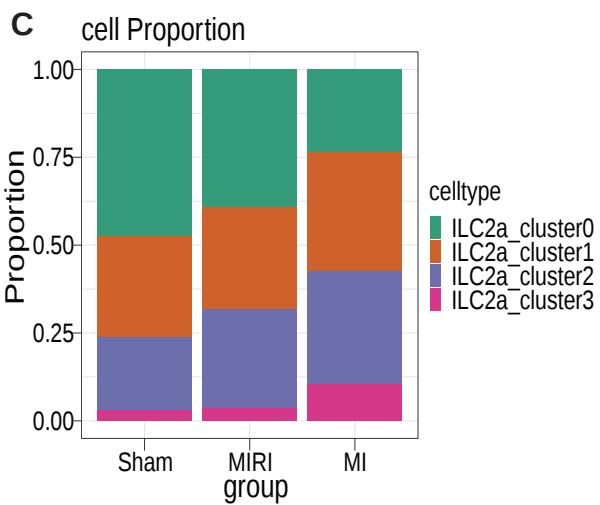
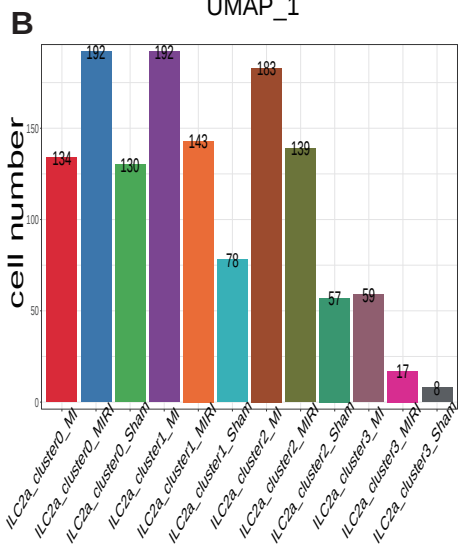
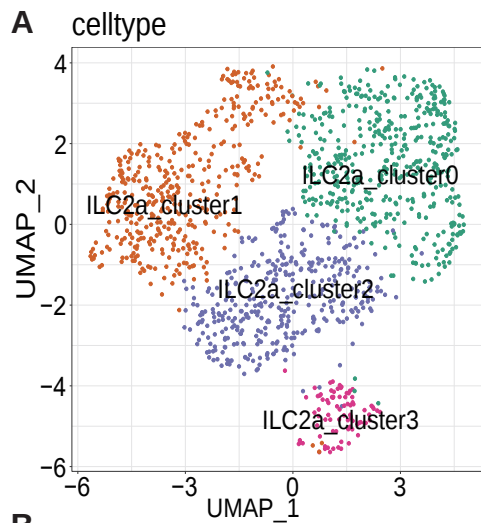
ILCdc_MI ILCdc_Sham pseudotime heatmap



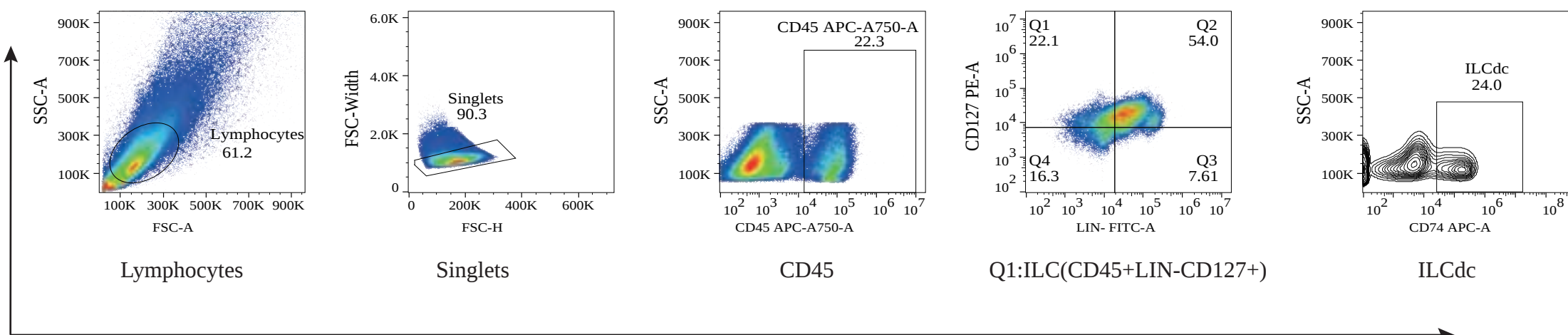
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ILCdc_MI ILCdc_Sham BEAM

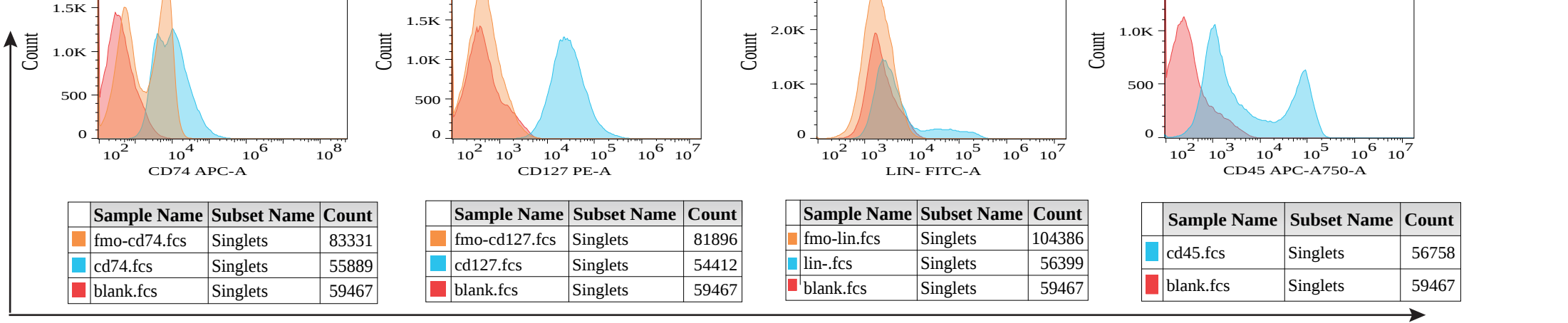




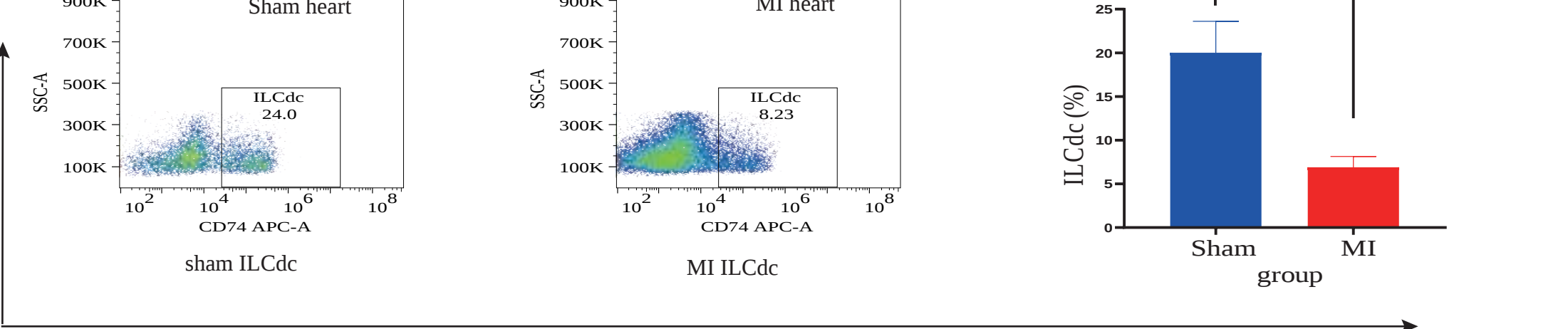
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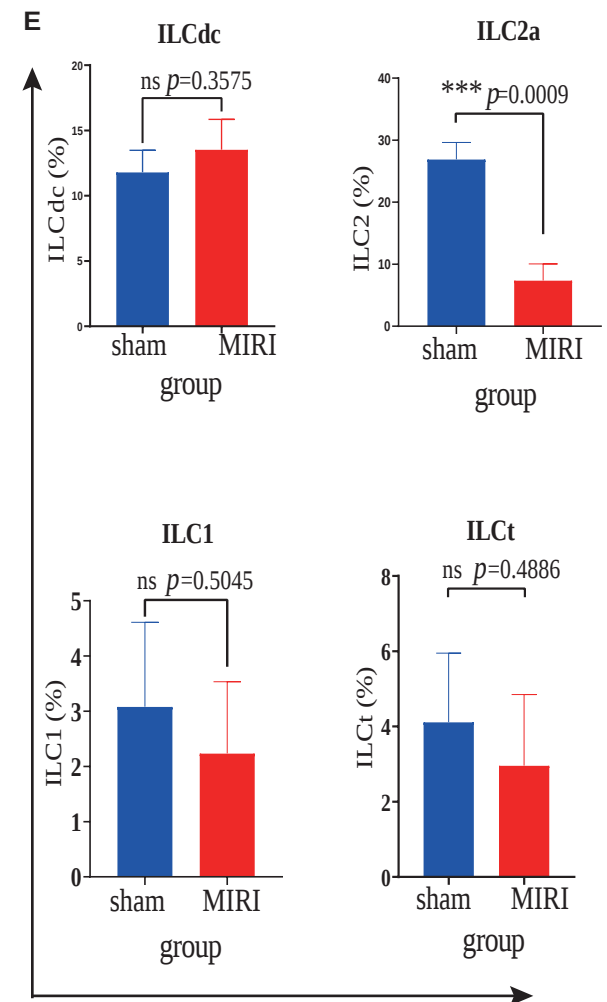
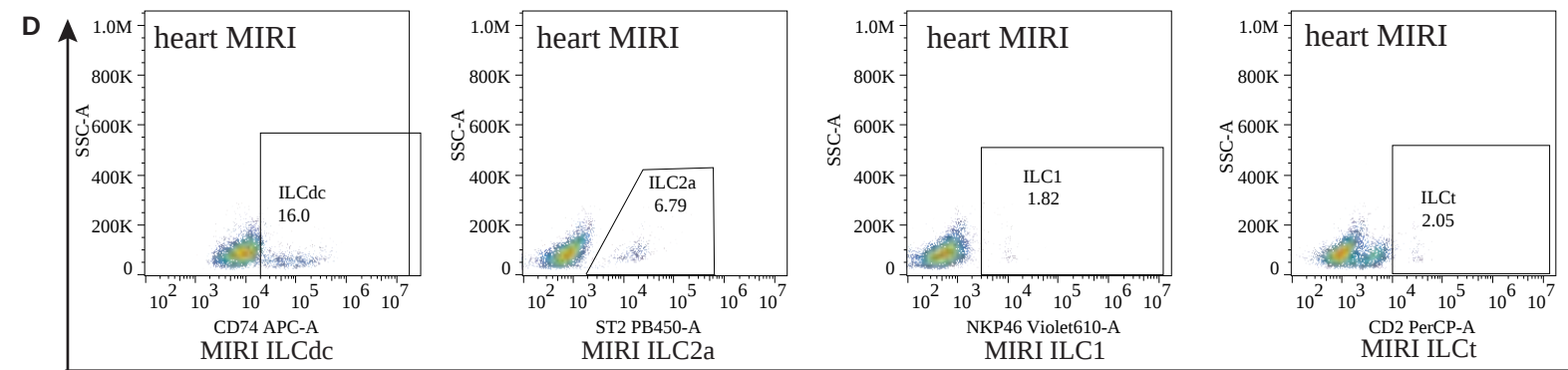
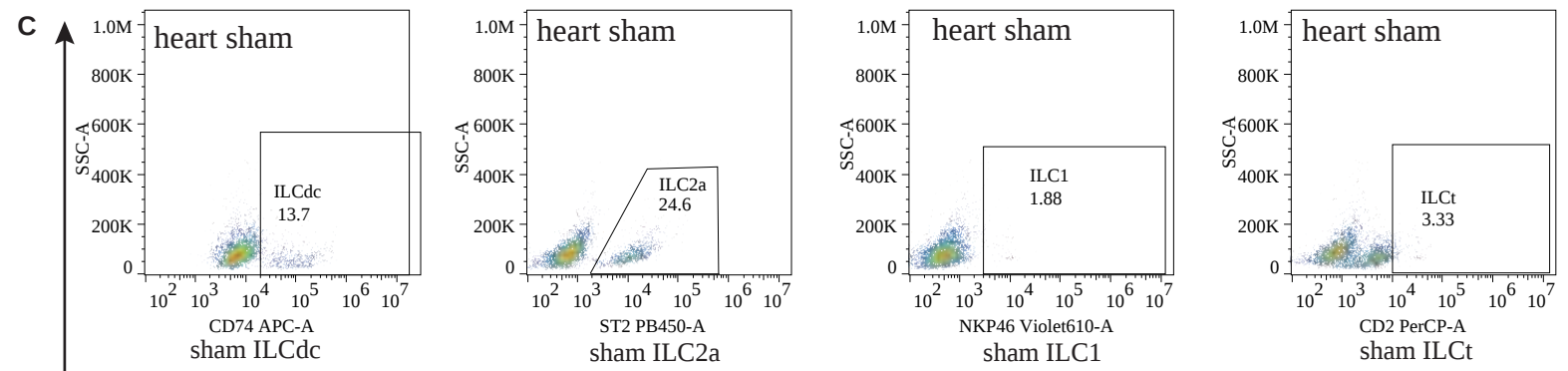
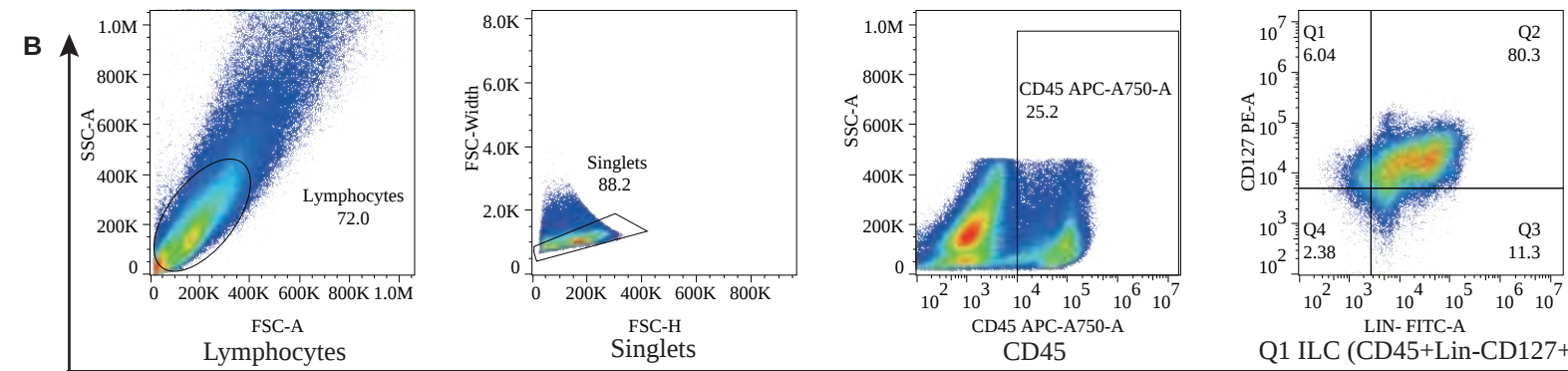
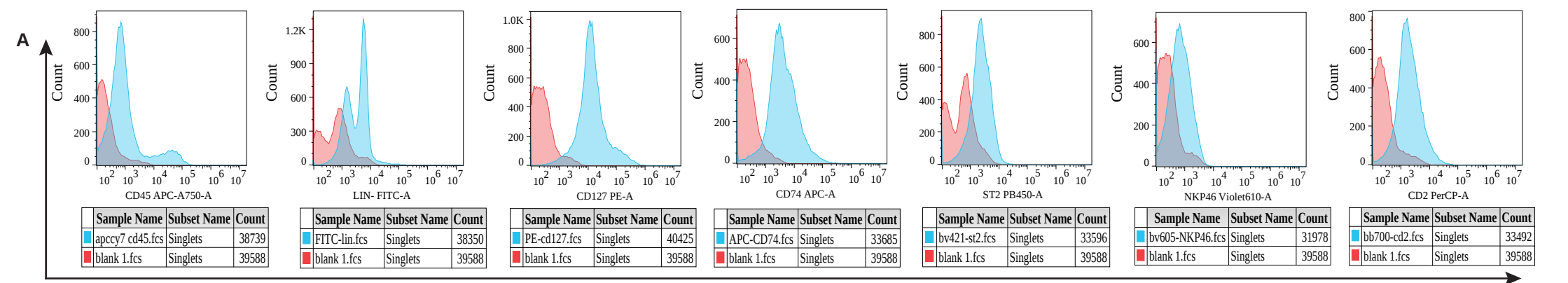


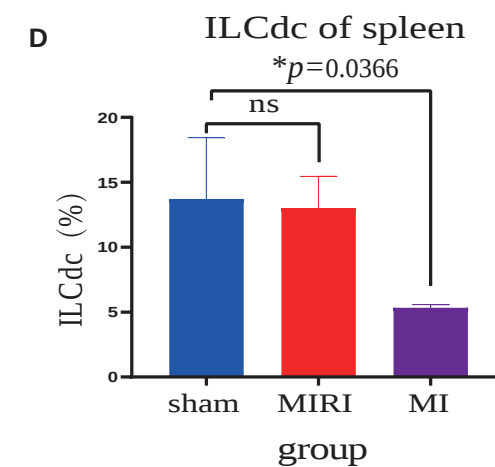
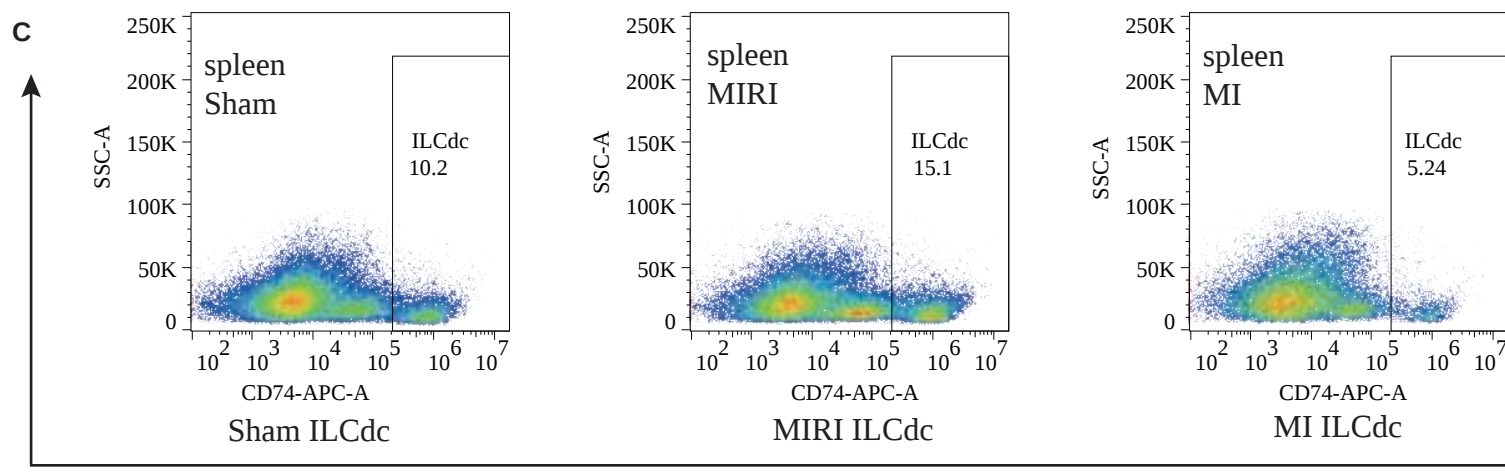
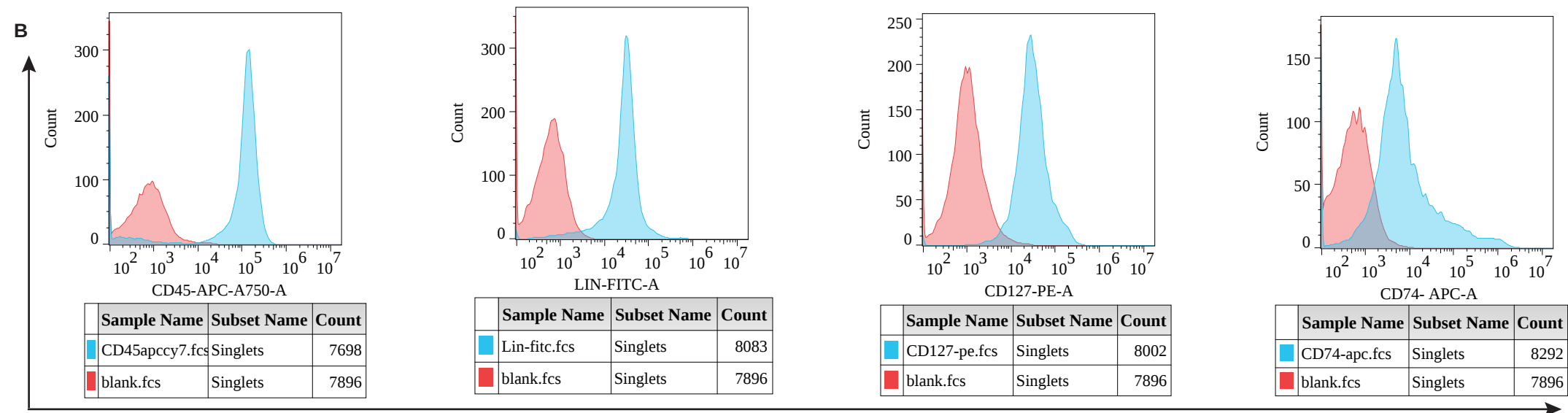
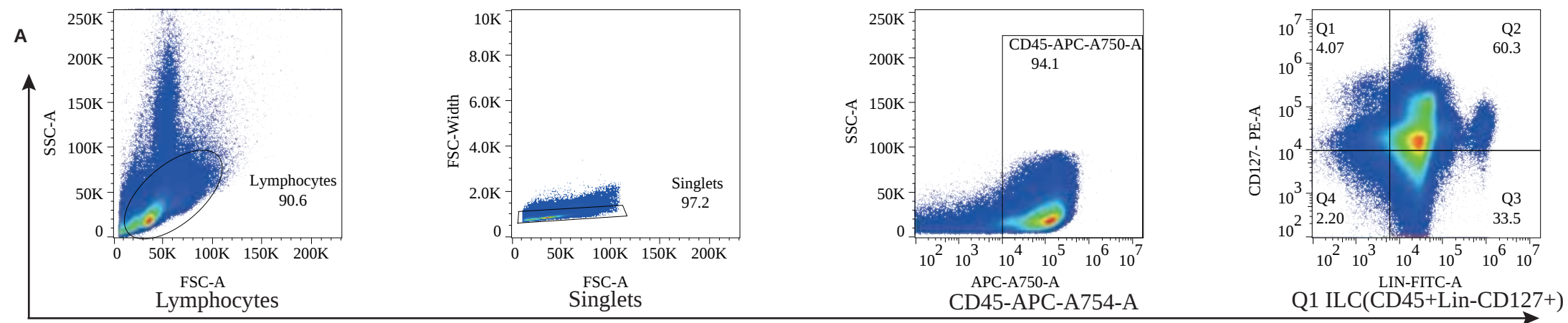
B



C







Supplementary figure legends

Fig S1. Flow Sorting, quality control and expression of some specific genes.

A-C. Typical flow cytometry graphs of ILCs sorting (Lin⁻CD45⁺CD127⁺) for sham (**A**), MIRI (**B**) and MI group (**C**). **D-E.** Violin plots show the nFeature_RNA, nCount_RNA and percent.MT for different groups before (**D**) and after (**E**) quality control. nFeature_RNA represents the number of genes measured in each cell; nCount_RNA represents the sum of all genes detected in each cell; percent.MT represents the proportion of mitochondrial genes detected and percent. **F.** Remove potential double cells (red dots) with R package DoubletFinder. **G-I.** Violin plots show the expression of ILCreg related genes, such as Id3 (**G**), Il1b (**H**) and Bcl2a1b (**I**). **J-L.** Feature plots show the expression of proliferation-related genes, such as Mki67 (**J**), Pcna (**K**) and Top2a (**L**).

Fig S2. Proportion changes, hdWGCNA analysis of hub genes, pathways and regulatory networks, BEAM analysis.

A. Bar plot visualizing the number of ILCs clusters in different disease groups, and stack plot visualizing the proportion of ILCs clusters in different disease groups. **B.** Top 10 genes in each module were identified by hdWGCNA analysis according to kME value. **C.** The modules are reassigned into 5 new clusters by “OverlapModulesDEGs” function and then annotate the 5 clusters by DEGs in ILCs. **D-E.** GO Biological process was shown in (**D**) and molecular function was shown in (**E**) to exhibit signal enrichments in special

modules. **F.** Network plot shows the hub genes of ILCdc (turquoise module), ILC2a (blue module) and ILC2b (pink module). **G.** Heatmap of the top 50 differential genes ($P < 0.01$) discovered in branch point 1 of sham group by the BEAM function.

Fig S3. Pseudotime analysis of ILCs clusters differentiation in MIRI and MI group.

A-B. Change trend of Cd74, Gata3, Pclaf, Trac and Xcl1 on pseudotime trajectory in the MIRI (**A**) and MI group (**B**). **C-D.** Displaying top 50 differential genes of pseudotime variation ($P < 0.01$) by clustering heatmap in the MIRI group (**C**) and MI group (**D**). **E-F.** Pseudotime kinetics of Cd74, Gata3, Pclaf, Trac and Xcl1 from the root to two branch points in the MIRI group (**E**) and MI group (**F**). **G-H.** Heatmap of the top 50 differential genes ($P < 0.01$) discovered in branch point 1 of MIRI group (**G**) and MI group (**H**) by the “BEAM” function with “monocle2”.

Fig S4. Analysis of ILCs clusters TF in sham and MIRI by SCENIC.

A-B. Use RSS to identify ILCs clusters specific regulons in the sham group (**A**) and in the MIRI group (**B**). The color depth represents the z-score value, and the size of the point represents the RSS score. **C-D.** Heatmaps show the binary converted regulators activated in the sham group (**C**) and in the MIRI group (**D**).

Fig S5. Intercellular communication among ILCs clusters in sham and MIRI groups.

A-B. Circos plots show the interactions of ligand-receptors across and within ILCs clusters in sham (**A**) and MIRI group (**B**). **C-D.** Bubble plots show the enrichment pathways of paired ligand-receptor data sets between signal sender and receiver in sham (**C**) and MIRI group (**D**). **E-F.** Heatmaps show the paired ligand-receptor involved between the signal sender and receiver cells in sham (**E**) and MIRI group (**F**). **G-H.** Sankey plots display the cell communications between ILC2a and ILCdc and downstream TFs in sham group (**G**) and MIRI group (**H**). **I.** Sankey plot displays the cell communications between ILCdc and ILC2b and downstream TFs in MI group. **J.** Sankey plot displays the cell communications between ILCdc and ILCdc and downstream TFs in MI group. **K-L.** Feature plots show the expression of Cxcl16 and Tgfb1.

Fig S6. Pseudotime analysis of ILCdc differentiation.

A. Heatmap displays several gene cohorts that changed during the pseudotime transition of the ILCdc sub-clusters in MI group. **B.** Heatmap of Top 50 significantly changed genes ($P < 0.01$) discovered by the BEAM function with monocle2 at branch point 1 of the ILCdc subclusters in MI group. **C.** Pseudotime analysis of ILCdc development and distribution between MI group and Sham group. **D.** Heatmap displays several gene cohorts that changed during the pseudotime transition in the ILCdc between MI group and Sham group. **E.** Heatmap of Top 50 significantly changed genes ($P < 0.01$) discovered by the BEAM function with monocle2 at branch point 1 of the ILCdc between MI group and Sham group.

Fig S7. The heterogeneities and transcriptional features of ILC2a.

A. Visualization of ILC2a Sub-clusters Infiltrated in ischemic Myocardium of Mice by UMAP. **B.** Bar plot shows the cell number of ILC2a sub-clusters in different disease groups. **C.** Stack plot visualizes the proportion of ILC2a Sub-clusters in different disease groups. **D.** Dot plot displays the marker genes of ILC2a Sub-clusters. **E.** Distribution statuses of ILC2a subclusters on pseudotime trajectory in the MI group. **F.** Heatmap displays several gene cohorts that changed during the pseudotime transition of the ILC2a sub-clusters in MI group. **G.** Heatmap of Top 50 significantly changed genes ($P < 0.01$) discovered by the BEAM function with monocle2 at branch point 1 of the ILC2a subclusters in MI group.

Fig S8. Identification of ILCdc in cardiac mononuclear cells by flow cytometry

A. Flow cytometric gating strategy of ILCdc ($\text{Lin}^- \text{CD45}^+ \text{CD127}^+ \text{CD74}^+$) in cardiac mononuclear cells, Q1 represents ILC ($\text{Lin}^- \text{CD45}^+ \text{CD127}^+$). **B.** The blank control fluorescence channel and the single antibody labeled fluorescence channel are shown by the histogram, red color represents the blank control fluorescence channel, blue color represents the CD74-APC, CD127-PE, Lin-FITC, CD45-APC-A750 fluorescence channel, respectively. The orange color represents the FMO control for CD74-APC, CD127-PE, and Lin-FITC, respectively. **C.** ILCdc ($\text{Lin}^- \text{CD45}^+ \text{CD127}^+ \text{CD74}^+$) was identified in cardiac mononuclear cells by flow cytometry, and the proportion of ILCdc in

the heart was shown in sham and MI groups, respectively. **D.** Comparison of ILCdc differences between sham and MI groups by two-tailed unpaired T test, n=3, 3-5 mice per sample, *represents a significant difference ($p<0.05$), **represents a significant difference ($p<0.01$), ns represents no significant difference.

Fig S9. ILC subsets in cardiac mononuclear cells in MIRI and sham group were identified by flow cytometry

A. The blank control fluorescence channel and single antibody labeled fluorescence channel are shown by histogram, red color represents the blank control fluorescence channel, The blue color represents the fluorescence channels of CD45-APC-A750, Lin-FITC, CD127-PE, CD74-APC, ST2-PB450, NKP46-Violet610, and CD2-Percp, respectively. The X-axis represents the value of the fluorescence channel, and the Y-axis represents the number of cells. **B.** Flow cytometric gating strategy of ILC(Lin⁻CD45⁺CD127⁺) in cardiac mononuclear cells, Q1 represents ILC(Lin⁻CD45⁺CD127⁺). **C-D.** Identification of ILCdc(Lin⁻CD45⁺CD127⁺CD74⁺), LC2a(Lin⁻CD45⁺CD127⁺ST2⁺), LC1 (Lin⁻CD45⁺CD127⁺NKP46⁺), ILCt(Lin⁻CD45⁺CD127⁺CD2⁺) in cardiac mononuclear cells by flow cytometry, Represents the proportions of ILCdc, ILC2a, ILC1, and ILCt in sham and MIRI groups, respectively. **E.** Comparison of ILCdc, ILC2a, ILC1, and ILCt between sham and MIRI groups by two-tailed unpaired T test, respectively, n=3, 3-5 mice per sample. * represents a significant difference ($p<0.05$), ** represents a significant difference ($p<0.01$), *** represents a significant difference ($p<0.001$), ****represents a

significant difference ($p < 0.0001$), ns represents no significant difference.

Fig S10. ILCdc in splenic mononuclear cells was identified by flow cytometry

A. Flow cytometric gating strategy of ILCs ($\text{Lin}^- \text{CD45}^+ \text{CD127}^+$) on splenic mononuclear cells, Q1 represents ILCs ($\text{Lin}^- \text{CD45}^+ \text{CD127}^+$). **B.** The blank control fluorescence channel and single antibody labeled fluorescence channel are shown by histogram, red color represents the blank control fluorescence channel, blue color represents the CD45-APC-A750, Lin-FITC, CD127-PE, CD74-APC fluorescence channel respectively, x axis represents the value of fluorescence channel, y axis represents the number of cells. **C.** ILCdc ($\text{Lin}^- \text{CD45}^+ \text{CD127}^+ \text{CD74}^+$) in splenic mononuclear cells was identified by flow cytometry, showing the proportion of ILCdc in sham, MIRI, and MI groups, respectively, and the gating strategy represents CD74^+ cells from Q1 ILC ($\text{Lin}^- \text{CD45}^+ \text{CD127}^+$). **D.** Comparison of ILCdc differences among sham, MIRI, and MI groups by one-way ANOVA, $n=3$, 3-5 mice per sample, * represents a significant difference ($p < 0.05$), ns represents no significant difference.